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Direct Synthesis of Mono-Glycosylated Catechols from Glycosylacetates or Imidates Using $BF_3.OEt_2$ as Catalyst[1]

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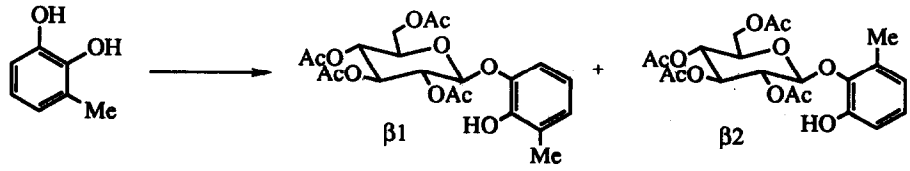
Abstract: *The coupling of 3-n-alkylcatechols to the acetate or trichloroimidate derivatives of β-D- or α-D- sugars (glucose, galactose, xylose, mannose and maltose) catalysed by $BF_3.OEt_2$ has been studied. β sugars with an equatorial acetate group at position 2 formed exclusively β adducts with yields of 60-80%. α sugars with an equatorial acetate group at position 2 formed β adducts, while β sugars with an axial acetate group formed α adducts when activated as trichloroimidates, with yields of 70-85%. Two mechanisms to explain these results are proposed.*

One of the preoccupations of the end of this century is to develop in vitro "alternative" tests to detect the pharmacological and toxic properties of xenobiotic molecules[2]. Although such tests have been established in certain areas, an in vitro test for the allergenising properties of molecules has yet to be developed. One obstacle to its development is that many allergens are hydrophobic and thus not water-soluble. During our studies of the mechanism of contact allergy, we have been confronted, for example, with the problem of dissolving in water highly hydrophobic molecules, such as the pentadecylcatechols, the principal allergens[3] of poison ivy and poison oak.

Amongst the different solutions envisaged for increasing the water-solubility of alkylcatechols, one which seems particularly attractive is the introduction of a sugar on the aromatic nucleus by means of an O-glycosidic link. The presence of a sugar should significantly increase the water-solubility of the molecule and sugars are not intrinsically cytotoxic, this being an important consideration for their subsequent in vitro use. In addition, the relative lability of the glycosidic link should release the unmodified allergen on contact with cells.

In the plant kingdom, many hydrophobic substances are found in solution in the form of glycosides[4], for example the tuliposides A and B which are hydrolysed to the tulipalines A and B, the principal allergens of the tulip bulb[5]. To our surprise, despite the existence of natural substances containing ß-glycosylated catechols[6], we were unable to find in the literature any method for the direct glycosylation of catechols. This might be explained by the extreme lability of these molecules which are highly sensitive to oxidation and particularly unstable in basic media. We have tested on the catechols those methods generally used for phenols using bromoacetoglycosides (not always easy for access and labile) in the presence of silver oxide (Koenigs-Knorr conditions)[7] and, more recently, in the presence of $Sn(OTf_2)$[8] or using phase-transfer conditions[9], as well as those methods described for diols Bu_2SnO[10]. Due to the lability of catechols (basic media or oxidants), the yields obtained have often been very low or even zero. We have therefore tried to couple directly ß-D-glucosepentaacetate to 3-methylcatechol, using acid catalysis ($BF_3.OEt_2$).

Table 1: Coupling reaction of 3-methylcatechol and glucose derivatives under various conditions.



Starting material	Reagent	Solvent	Yield[a]	β1/β2[b]
β-D-Glc(OAc)$_4$Br	$Sn(OTf)_2$	CH_2Cl_2	32%	20/80
β-D-Glc(OAc)$_4$Br	Bu_2SnO	toluene	60%	100/0
β-D-Glc(OAc)$_4$Br	Ag_2O	CH_2Cl_2/toluene	0%	-
β-D-Glc(OAc)$_4$Br	Phase transfer	$CHCl_3/OH^-$	10%	90/10
β-D-Glc(OAc)$_5$	$BF_3.OEt_2$	toluene	65%	91/9

a) Based on isolated compounds; b) Ratio of anomeric protons determined by ^1H NMR.

It is clear from Table 1 that the use of $BF_3.OEt_2$ with ß-pentaacetylated sugars could be a simple and rapid method of preparation of glycosylated derivatives of catechols[11]. It is relatively easy and applicable to large scale starting from precursors either available commercially or by simple acetylation of the corresponding sugars. In order to optimise the coupling reaction, we then studied the effects of solvent, temperature and time of reaction on the yield of the reaction product and the ß1/ß2 ratio. The two isomers are in all cases separable by column chromatography over SiO_2.

Influence of the solvent. The coupling reaction of the model substrate 3-methylcatechol to ß-Glc(OAc)$_5$ and ß-Gal(OAc)$_5$ in the presence of $BF_3.OEt_2$ was carried out in various solvents at 25°C. In complexing solvents, such as ethyl ether or THF, no coupling was observed. This was also the case in DMF or acetonitrile. Optimal yields were obtained in methylene chloride or toluene, the latter being slightly greater; however, methylene chloride seemed to us to be more convenient to use.

Table 2: Influence of the solvent on the yield of glycosylation.

Solvent	β-Glc(OAc)$_5$	β-Gal(OAc)$_5$
toluene	65% (91/9)[a]	81% (87/13)
CH_2Cl_2	61% (82/18)	76% (88/12)

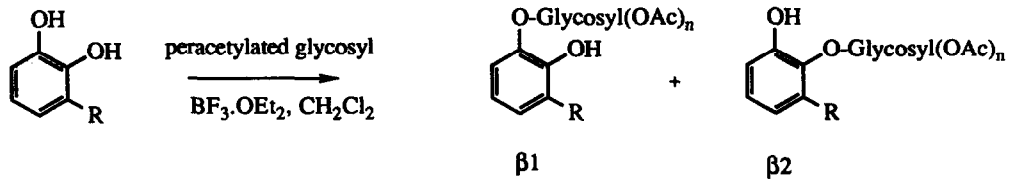
a) β1/β2 ratio.

Influence of temperature. We then looked at the effect of temperature on the coupling reaction in methylene chloride of the model substrate 3-methycatechol to ß-Glc(OAc)$_5$ and ß-Gal(OAc)$_5$ in the presence of $BF_3.OEt_2$. Despite substantially longer reaction times, useful yields were only obtained at or above 25°C. It should be noted that increasing the temperature, while giving higher yields (76% yield for β-Glc(OAc)$_5$), also resulted in a lower ß1/ß2 ratio, which, for glucose, was essentially constant (80/20) up to 25°C but fell to only 60/40 on refluxing.

Optimal conditions having been established as 1 hour in methylene chloride at 25°C, we then used them for the coupling to sugar derivatives of different 3-n-alkylcatechols with increasingly longer chains. The yields and the ß1/ß2 ratios are shown in table 3. Yields were not influenced by chain length, while the ß1/ß2 ratio

increased with the number of carbons and bulkiness. Coupling a disaccharide such as maltose was also very simple, giving a yield of 65%.

Table 3: Coupling reaction of 3-n-alkylcatechols and peracetylated glycosyls using $BF_3.OEt_2$.



β1 β2

R	β-Glc(OAc)$_5$	β-Gal(OAc)$_5$	β-Xyl(OAc)$_5$	β-Man(OAc)$_5$	β-Maltose(OAc)$_8$
CH_3	61% (82/18)[a]	76% (88/12)	64% (80/20)	12% (100/0)[b]	-
C_5H_{11}	67% (88/12)	72% (89/11)	-	-	-
$C_{10}H_{21}$	63% (92/8)	68% (95/5)	-	-	-
$C_{15}H_{31}$	62% (96/4)	77% (97/3)	79% (96/4)	5% (100/0)[a]	65% (99/1)

a) β1/β2 ratio; b) Only the α adduct was observed.

In all cases, ß adducts were formed, except for mannose where only the α adduct was obtained in low yield (12%). Tests performed in another context using pentaacetylated sugars of α configuration yielded ß adducts, but again only in very low yield (5-10%). It is known that equatorial acetate groups at position 2 of sugars can have a very important assisting role during anomeric reactions[12]. In the case of the ß derivative of glucose, galactose, xylose and maltose, it can be imagined that the acetate group at position 2 aids the departure of the anomeric acetate to form an intermediate which can only formed a ß adduct by the attack of one of the oxygens of the catechol. This mechanism is no longer possible if the acetate at position 2 is axial (mannose) or if the sugar has an α configuration, thus explaining the low yields obtained.

The replacement of acetate groups in the anomeric position with better leaving groups, such as trichloroacetoimidates, could possibly compensate for the lack of assistance of acetate at position 2. In point of fact, trichloroacetoimidates have been described in the coupling of benzylated sugars where no such assistance is possible[13].

Table 4: Coupling reaction of 3-n-alkylcatechols and glycosyl trichloroacetoimidates using $BF_3.OEt_2$.

R	α-Glc(OAc)$_5$	α-Glc(OAc)$_4$-Imidate[a]	β-Man(OAc)$_4$-Imidate[a]
CH_3	30% (91/9)[b]	78% (91/9)	85% (100/0)[c]
$C_{15}H_{31}$	-	-	70% (100/0)[c]

a) Trichloroacetoimidate derivative; b) β1/β2 ratio; c) Only the α adduct was observed.

We therefore tried to link catechols to trichloroimidate derivatives of sugars, which can be easily prepared in two steps from the pentaacetate derivatives. Under similar reaction conditions to those used for the acetates, the trichloroacetoimidate derivative of α-D-glucose gave the ß conjugate with a yield of 78% and the trichloroacetoimidate derivative of ß-D-mannose the α conjugate with a yield of 85%.

In this case, we imagine that the reaction proceeds via an oxonium intermediate. In the presence of an equatorial acetate group at position 2, this oxonium would form the same intermediate as before and lead to the ß adduct, whereas with an axial non-participating acetate group only the α adduct would be formed.

We have therefore demonstrated that $BF_3.OEt_2$ can efficiently catalyse the coupling of the acetylated derivatives of sugars to catechols, forming monoadducts in high yield and that it is possible to compensate for the lack of assistance of acetate at position 2 by a trichloroacetoimidate group.

References and notes

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11. All compounds were fully characterized and gave satisfactory microanalysis. In a typical procedure: To 3-n-methylcatechol 2.48 g; 20 mmol) in CH_2Cl_2 (40 mL) and 4 Å molecular sieves was added β-D-glucopyranosepentaacetate (8 g; 20 mmol, 1 eq) and $BF_3.OEt_2$ (2.1 mL; 16 mmol; 0.8 eq). The reaction mixture was stirred at room temperature for 1 h and hydrolysed with water (2 mL). The organic solution was washed with water, brine and dried over $MgSO_4$. Organic solvents were removed under vacuum and the crude adduct purified by column chromatography over SiO_2 (30% AcOEt, hexane) to give 5.3 g (11.3 mmol) of the catechol adduct β1 and 1.2 g (2.7 mmol) of the catechol adduct β2 as white solids.
    1-(O-β-D-glucopyrannoside tetraacetate)-3-methylcatechol: ^1H NMR (400 MHz, CD_2Cl_2) δ 6.84 (d, 1H, H_3, J_{H2-H3}=7.52Hz), 6.79 (d, 1H, H_1,J_{H1-H2}=8.1Hz), 6.69 (dd t like, 1H, H_2), 6.04 (s, 1H, OH), 5.32 (dd, 1H, $H_{3'}$), 5.23 (dd, 1H, $H_{2'}$, $J_{H2'-H3'}$=9.9Hz, $J_{H2'-H1'}$=7.8Hz), 5.13 (dd, 1H, $H_{4'}$, $J_{H3'-H4'}$=9.3Hz, $J_{H5'-H4'}$=10.0Hz), 4.98 (d, 1H, $H_{1'}$), 4.26 (dd, 1H, $H_{6'a}$, $J_{H6'a-H5'}$=5.70Hz, $J_{H6'a-H6'b}$=12.32Hz), 4.17 (dd, 1H, $H_{6'b}$, $J_{H6'b-H5'}$=2.44Hz), 3.88 (ddd, 1H, $H_{5'}$), 2.22 (s, 3H, CH_3-Ar), 2.09 (s, 3H, CH_3-CO), 2.07 (s, 3H, CH_3-CO), 2.03 (s, 6H, CH_3-CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.08 (CO), 169.71 (CO), 169.57 (CO), 169.07 (CO), 145.15 (C2), 143.71 (C1), 126.08 (C4), 125.31 (C3), 118.93 (C5), 114.57 (C6), 101.00 (C1'), 72.08 (C3'), 71.77 (C5'), 71.12 (C2'), 68.01 (C4'), 61.57 (C6'), 20.27 (CH_3-CO), 20.17 (CH_3-CO), 20.11 (2 CH_3-CO), 15.28 (CH_3). Anal. Calcd. for $C_{21}H_{26}O_{11}$: C, 55.54; H, 5.77. Found: C, 55.58; H, 5.73.
    2-(O-β-D-glucopyrannoside tetraacetate)-3-methylcatechol: ^1H NMR (400 Mhz, $CDCl_3$) δ 6.92 (dd t like, 1H, H_2), 6.76 (dd, 1H, H_1, J_{H1-H3}=1Hz, J_{H1-H2}=7.6Hz), 6.65 (dd, 1H, H_3, J_{H3-H2}=7.35Hz), 6.09 (s, 1H, OH), 5.29 (dd, 1H, $H_{3'}$, $J_{H3'-H4'}$=9.4Hz), 5.23 (dd, 1H, $H_{2'}$, $J_{H2'-H3'}$=9.8Hz), 5.13 (dd t like, 1H, $H_{4'}$), 4.78 (d, 1H, $H_{1'}$, $J_{H1'-H2'}$=7.9Hz), 4.24 (dd, 1H, $H_{6'a}$, $J_{H6'a-H6'b}$=12.4 Hz, $J_{H6'a-H5'a}$=5.6Hz), 4.09 (dd, 1H, $H_{6'b}$, $J_{H6'b-H5'}$=2.4Hz), 3.74 (ddd, 1H, $H_{5'}$, $J_{H5'-H4'}$=9.9Hz); 2.18 (s, 3H, CH_3-Ar); 2.08 (s, 3H, CH_3-CO); 2.06 (s, 3H, CH_3-CO); 2.03 (s, 3H, CH_3-CO), 2.00 (s, 3H, CH_3-CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.42(CO), 170.39 (CO), 169.17 (CO), 168.93 (CO), 149.46 (C2), 142.45 (C1), 131.34 (C4), 126.19 (C3), 122.06 (C5), 114.95 (C6), 102.63 (C1'), 72.52 (C3'), 72.14 (C5'), 71.13 (C2'), 67.96 (C4'), 61.34 (C6'), 20.51 (CH_3-CO), 20.46 (CH_3-CO), 20.39 (2 CH_3-CO), 15.90 (CH_3).
    1-(O-α-D-mannopyrannoside tetraacetate)-3-pentadecylcatechol: ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, 1H, H_3, J_{H3-H2}=8.2 Hz, J_{H3-H1}=1.1Hz), 6.85 (dd, 1H, H_1, J_{H1-H2}=7.7Hz), 6.73 (dd tlike, 1H, H_2), 5.72 (s, 1H, OH), 5.50 (m, 2H, $H_{2'}$ + $H_{3'}$), 5.46 (d, 1H, $H_{1'}$, $J_{H1'-H2'}$=1.7Hz), 5.37 (ddd, 1H, $H_{4'}$, $J_{H4'-H3'}$=10.1Hz, $J_{H4'-H5'}$=9.5Hz, $J_{H4'-H6'a}$=1.3Hz), 4.29 (ddd, 1H, $H_{6'a}$, $J_{H6'a-H5'}$=6.2Hz, $J_{H6'a-H6'b}$=12.4Hz), 4.16 (ddd, 1H, $H_{5'}$), 4.12 (dd, 1H, $H_{6'b}$, $J_{H6'b-H5'}$=2.2Hz), 2.62 (t, 2H, CH_2-Ar), 2.07 (s, 6H, 2 x CH_3-CO), 2.04 (s, 6H, 2 x CH_3-CO), 1.61 (m, 2H, CH_2-CH_2Ar), 1.26 (m, 24H, CH_2), 0.88 (t, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.56 (CO), 170.15 (CO), 169.97 (CO), 169.75 (CO), 143.76 (C2), 143.14 (C1), 130.38 (C3), 124.80 (C4), 119.48 (C5), 113.03 (C6), 91.28 (C1'), 69.39 (C3'), 69.26 (C5'), 68.94 (C2'), 65.97 (C4'), 62.14 (C6'), 31.90, 29.89, 29.67 (8C), 29.56 (2C), 29.33, 22.67 , 20.78 (2 CH_3-CO), 20.64 (2 CH_3-CO), 14.09 (CH_3). Anal. Calcd. for $C_{35}H_{54}O_{11}$: C, 64.59; H, 8.36. Found: C, 64.78; H, 8.41.
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